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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/658,659	09/08/2000	Vincent P. Stanton JR.	11926-015001	3340

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EXAMINER	
MYERS, CARLA J	
ART UNIT	**PAPER NUMBER**
1634	

DATE MAILED: 06/24/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/658,659	STANTON, VINCENT P.	
	Examiner	Art Unit	
	Carla Myers	1634	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☐ Responsive to communication(s) filed on _____.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) 182-201 is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) 182-201 is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

1. The allowability of claims 182-201 is withdrawn. As indicated in the letter of April 20, 2004, prosecution in this application is being re-opened. Upon further consideration, the following grounds of rejection are being applied. This action is made non-final.

Claim Rejections - 35 USC § 112

2. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 182-201 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for (i) probes consisting of 15 or more contiguous nucleotides of SEQ ID NO: 1 wherein the 15 or more contiguous nucleotides includes nucleotide position 668 of SEQ ID NO: 1, with the exception that at nucleotide position 668 C is replaced by T; (ii) probes consisting of 15 or more contiguous nucleotides of SEQ ID NO: 1 wherein the 15 or more contiguous nucleotides includes nucleotide position 1298 of SEQ ID NO: 1, with the exception that at nucleotide position 1298 C is replaced by A; and (iii) methods comprising contacting a test sample with the probes of (i) or (ii) and detecting hybridization between said probes and nucleic acid present in the test sample, does not reasonably provide enablement for probes comprising at least 15 contiguous nucleotides of SEQ ID NO: 1 comprising at least one or two of a C

at nucleotide 120, a G at nucleotide 464, a T at nucleotide 519, a T at nucleotide 668 a C at nucleotide 1059, an A at nucleotide 1289, a C at nucleotide 1308, and an A at nucleotide 1784. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims.

The following factors have been considered in formulating this rejection (*In re Wands,* 858F.2d 731, 8 USPQ2d 1400 (Fed. Cir. 1988): the breadth of the claims, the nature of the invention, the state of the prior art, the relative skill of those in the art, the predictability or unpredictability of the art, the amount of direction or guidance presented, the presence or absence of working examples of the invention and the quantity of experimentation necessary.

The claims are drawn to nucleic acid probes comprising at least 15 contiguous nucleotides of SEQ ID NO: 1, said probes comprising at least one of or at least two of: nucleotide 120 of SEQ ID NO: 1 wherein T is replaced by C; nucleotide 464 of SEQ ID NO: 1 wherein T is replaced by G; nucleotide 519 of SEQ ID NO: 1 wherein C is replaced by T; nucleotide 668 of SEQ ID NO: 1 wherein C is replaced by T; nucleotide 1059 of SEQ ID NO: 1 wherein T is replaced by C; nucleotide 1289 of SEQ ID NO: 1 wherein C is replaced by A; nucleotide 1308 of SEQ ID NO: 1 wherein T is replaced by C; and nucleotide 1784 wherein G is replaced by A.

The specification is not enabling for the invention as it is broadly claimed for the following reasons:

1) The specification teaches the human MTHFR gene which consists of SEQ ID NO: 1 and the prior art of Rozen (WO 95/33054; cited in the IDS) teaches the porcine MTHFR gene. The specification (page 105) states that "Other investigators have identified variances in MTHFR, methionine synthase and folate receptor. These findings are summarized in Table 3." Table 3 lists the following variances in the MTHFR gene: C or T at position 129; C or T at position 677, C or T at position 1068, a C or A at position 1298 and a T or C at position 308. [It is noted that Applicant's amended the specification and Sequence Listing to modifying the numbering of the nucleotide positions of the MTHFR gene in the response of November 13, 2002. The C677T and C1298A variations listed in Table 3 are equivalent to the claimed C668T and C1289A variations.] Additionally, the specification (see Table 10) discloses a T to G variation at nucleotide position 464 and a G to A variation at nucleotide position 1784 of SEQ ID NO: 1.

However, as broadly written the claims encompass nucleic acids that are defined in terms of only 15 nucleotides. The identity and number of nucleotides flanking the 15mers are not defined. Further, the claims do not clearly set forth the relationship between the stated nucleotide and the probe. The claims as written do not require that the probe comprises a 15 mer consisting of, e.g. the C at nucleotide 120 and the 14 contiguous nucleotides surrounding nucleotide position 120 of SEQ ID NO: 1. Rather, the claims are inclusive of probes that comprise, e.g., 15 contiguous nucleotides of SEQ ID NO: 1 and a C. Because the claims do not define the flanking sequences and do not clearly set forth the

context of the nucleotide variation, the claims encompass homologs of the MTHFR gene, functionally similar and functionally distinct variants of the MTHFR gene, splice variants of the MTHFR gene, and unrelated synthetic or naturally occurring genes that contain a 15 mer fragment of SEQ ID NO: 1. The specification as originally filed does not teach an adequate number of species within the broadly claimed genus of probes. The specification teaches only the human MTHFR of SEQ ID NO: 1 and nucleotide substitutions at specific positions within SEQ ID NO: 1. It is unpredictable as to how the addition of nucleotides of any length and identity will effect the functional properties of a probe comprising 15 nucleotides of SEQ ID NO: 1. The specification does not provide sufficient guidance as to how to make and use the broadly claimed genus of probes for a practical purpose. Extensive experimentation would be required to determine which nucleotides and how many nucleotides may be added to 15 mer fragments of SEQ ID NO: 1 without altering the functional properties of the probes, e.g., without modifying the specific hybridization properties of the probe. As stated in the specification (for example, page 91), the probes are to be used to detect the presence or absence of specific variances as a means to predict a patient's response to treatment. However, the specification has not provided sufficient guidance as to how to use probes that comprise 15 nucleotides of SEQ ID NO: 1, but which significantly differ from SEQ ID NO: 1 with respect to their overall nucleotide structure. Further, the specification does not identify any additional homologs, insertion, substitution and deletion mutants, or splice variants of the MTHFR gene. The general knowledge in the art

concerning MTHFR nucleic acid probes and variants does not provide any indication of how the structure of one MTHFR nucleic acid (i.e., SEQ ID NO: 1) is representative of additional MTHFR homologs, mutant and splice variants. The structure and function of one molecule does not provide guidance as to the structure and function of other molecules. Therefore, the description of one human MTHFR nucleic acid (and one porcine MTHFR nucleic acid) and of 8 specific MTHFR point polymorphisms is not representative of the broadly claimed genus of probes in which only 15 nucleotides are defined and the flanking nucleotides are not defined and in which the functional properties of the resulting probe are also not defined.

2) The prior art enables the use of probes consisting of 15 or more contiguous nucleotides of SEQ ID NO: 1 wherein the probes differ from SEQ ID NO: 1 in that they contain a T at nucleotide position 668 or an A at nucleotide position 1289. Specifically, the prior art of Rozen (WO 95/33054; pages 30-31 and 35-36) teaches that the MTHFR 668T polymorphism (referred to therein as "677T") is associated with decreased MTHFR activity. van der Put (see abstract) teaches that homozygosity for the 668T polymorphism is associated with increased risk for developing neural-tube defects. The reference also teaches that combined heterozygosity for the 1289C (referred to therein as "1298C") and 668T polymorphisms provides an additional genetic risk factor for NTD. However, the specification does not adequately teach how to use probes containing a C at nucleotide 120, a G at nucleotide 464, a T at nucleotide 619, a C at nucleotide 1059, a C at nucleotide 1308 or an A at nucleotide 1784 of SEQ ID NO: 1. The

specification does not teach how each of these variations effects the activity of MTHFR and/or does not teach an association between these variations and the occurrence of any particular disorder or response to treatment. The specification teaches that the probes are to be used in diagnostic tests to predict a patient's response to treatment. Yet, the specification does not teach an association between these MTHFR variants and response to treatment. Rather, the specification sets forth a research method by which one would determine whether each individual variant or combination of variants effects a patient's response to treatment. It is highly unpredictable as to which variants or combinations of variants will be associated with response to therapy or with some an unstated disease or condition. The unpredictability in the art of using nucleotide variations to predict a patient's response to treatment or to predict the likelihood that an individual will develop a disease is supported by the teachings in the specification. At page 92, the specification states:

"Usually, variation in activity due to a single gene or a single genetic variance in a single gene is not sufficient to account for observed variation in patient response to treatment, e.g., a drug, there are often other factors that account for some of the variation in response. This is to be expected as drug response phenotypes usually vary continuously, and such (quantitative) traits are typically influenced by a number of genes...Although it is impossible to determine *a priori* the number of genes influencing a quantitative trait, often only a few loci have large effects...The sequential testing for correlation between phenotypes of interest and single nucleotide polymorphisms may be adequate to detect associations if there are major effects associated with single nucleotide changes; certainly it is useful to this type of analysis. However there is no way to know in advance whether there are major phenotypic effects associated with single

nucleotide changes and, even if there are, there is no way to be sure that the salient variance has been identified by screening cDNAs."

With respect to haplotypes, the specification (page 138) teaches that "(t)he biological effect of each variance at a locus may be different both in magnitude and direction. For example, a polymorphism in the 5' UTR may affect translational efficiency, a coding sequence polymorphism may affect protein activity, a polymorphism in the 3' UTR may affect mRNA folding and half life, and so on. Further, there may be interactions between variances..."

Thereby, the specification teaches in the absence of information regarding the functional effect of a polymorphism, it is not possible to predict the effect of a polymorphism or combination of polymorphisms on the occurrence of disease or the response to therapy. The specification emphasizes the need to perform experiments to determine the effect of a polymorphism or combination of polymorphisms before one can determine if there is an association between the polymorphism or combination of polymorphisms and the occurrence of disease or response to therapy.

Case law has established that "(t)o be enabling, the specification of a patent must teach those skilled in the art how to make and use the full scope of the claimed invention without 'undue experimentation.'" *In re Wright* 990 F.2d 1557, 1561. *In re Fisher,* 427 F.2d 833, 839, 166 USPQ 18, 24 (CCPA 1970) it was determined that "(t)he scope of the claims must bear a reasonable correlation to the scope of enablement provided by the specification to persons of ordinary skill in the art". The amount of guidance needed to enable the invention

is related to the amount of knowledge in the art as well as the predictability in the art Furthermore, the Court in *Genetech Inc. v Novo Nordisk* 42 USPQ2d 1001 held that "(I)t is the specification, not the knowledge of one skilled in the art that must supply the novel aspects of the invention in order to constitute adequate enablement". In the instant case, the state of the art indicates that it is unpredictable as to how the polymorphisms and combinations of polymorphisms at positions 120, 464, 519, 1059, 1308 and 1784 will effect MTHFR activity and as to whether these polymorphisms or combinations of polymorphisms will be associated with the occurrence of disease or response to therapy. Further, such information can only be obtained through random, trail-by-error experimentation. Additionally, the specification does not adequately teach one how to make and use a representative number of probes within the broadly claimed genus of probes comprising 15 nucleotides of SEQ ID NO: 1 and containing the stated polymorphisms. In view of the unpredictability in the art and the lack of specific guidance provided in the specification, undue experimentation would be required for one of skill in the art to practice the invention as it is broadly claimed.

3. The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 182-201 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claims 182-201 are indefinite because it is unclear as to what is intended to be the relationship between the stated nucleotide and the remainder of the

probe. It is unclear as to whether, for example, the probe comprises the 14 contiguous nucleotides surround nucleotide 120 of SEQ ID NO: 1 or whether the probe comprises 15 contiguous nucleotides of SEQ ID NO: 1 and includes a C. The limitation that the probe comprises "at least one of: nucleotide 120 of SEQ ID NO: 1" does not clarify the relationship of the nucleotide with respect to the claimed probe.

Claims 184-187 and 194-197 are indefinite over the recitations of "comprising no more than 500 contiguous nucleotides," "comprising no more than 200 contiguous nucleotides," "comprising no more than 100 contiguous nucleotides," and "comprising no more than 50 contiguous nucleotides." The claims include probes that contain at least 2 polymorphisms. Yet, the combinations of many of the polymorphisms at are distances greater than 500, 200, 100 or 500 nucleotides. For example, the claims include probes that comprise a polymorphism at position 120 and at 1784, yet the probe may not contain more than 50, 100, 200 or 500 nucleotides of SEQ ID NO: 1. It is unclear as to how such probes can contain both of the polymorphisms and still be of a length less than 50, 100, 200 or 500 nucleotides unless the probes do not contain contiguous fragments of SEQ ID NO: 1. Accordingly, it is unclear as to whether the claims are intended to be limited to probes which comprise contiguous sequences of SEQ ID NO: 1 or whether the claims encompass probes which contain fragments of SEQ ID NO: 1 and these fragments are not necessarily contiguous.

Claim Rejections - 35 USC § 102

4. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Claims 182, 184, 185, and 188 are rejected under 35 U.S.C. 102(b) as being anticipated by Rozen (WO 95/33054; cited in the IDS).

Rozen (see page 29) teaches an isolated MTHFR nucleic acid which contains a C to T substitution at nucleotide position 677. This substitution results in an alanine to valine change in the amino acid sequence (see page 29 and Figure 5A). The C677T polymorphism disclosed by Rozen is identical to the presently claimed C668T polymorphism (see Table 3 of the specification and the 132 Declaration of Dr. Stanton filed November 13, 2002 regarding the numbering of the nucleotides in SEQ ID NO: 1). Rozen teaches that the 677T (668T) polymorphism encodes for a thermolabile MTHFR protein having decreased MTHFR activity (pages 30-31 and 35-36). The reference (page 5) also teaches the use of probes for identifying MTHFR sequence abnormalities and specifically teaches the use of allele specific oligonucleotide hybridization probes (page 18). With respect to claims 18, 185 and 188, Rozen teaches a PCR fragment of 198bp that contains the 677T polymorphism (see page 29).

5. Claims 182-185, and 188 are rejected under 35 U.S.C. 102(b) as being anticipated by van der Put (American Journal of Human Genetics (1998) 62: 1044-1051).

It is noted that a claim as a whole is assigned an effective filing date (rather than the subject matter within a claim being assigned individual effective filing dates). The priority applications filed prior to June 15, 2000 do not disclose, for example, the MTHFR polymorphisms at positions 519 and 1784. Accordingly, the present claims are entitled to the priority date of June 15, 2000.

van der Put (see Table 1 and page 1045) teaches an isolated MTHFR nucleic acid which contains either an A or a C at nucleotide position 1298. The 1298 polymorphism disclosed by van der Put is identical to the presently claimed C1289A polymorphism (see the 132 Declaration of Dr. Stanton filed November 13, 2002 regarding the numbering of the nucleotides in SEQ ID NO: 1). Van der Put (page 1246) also teaches isolated MTHFR nucleic acids which contain both a T at position 677 (668) and an A at position 1298 (1289). With respect to claims 18, 185 and 188, van der Put teaches a PCR fragment of 163 bp that contains the 1298A (1289A) polymorphism (see page 1045).

Claim Rejections - 35 USC § 103

6. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claims 186-187, 189-192 and 194-201 are rejected under 35 U.S.C. 103(a) as being unpatentable over by Rozen in view of Carlsson (U.S. Patent No. 6,020,126).

Rozen (see page 29) teaches an isolated MTHFR nucleic acid which contains a C to T substitution at nucleotide position 677. This substitution results in an alanine to valine change in the amino acid sequence (see page 29 and Figure 5A). The C677T polymorphism disclosed by Rozen is identical to the presently claimed C668T polymorphism (see Table 3 of the specification and the 132 Declaration of Dr. Stanton filed November 13, 2002 regarding the numbering of the nucleotides in SEQ ID NO: 1). Rozen teaches that the 677T (668T) polymorphism encodes for a thermolabile MTHFR protein having decreased MTHFR activity (pages 30-31 and 35-36). Rozen also teaches a PCR fragment of 198bp that contains the 677T polymorphism (see page 29) and teaches PCR/restriction enzyme analysis to detect the presence of the MTHFR 677T (668T) polymorphism. Rozen does not specifically exemplify hybridization methods using a probe containing the 677T (668T) polymorphism.

However, Rozen (page 5) does teach the general use of probes for identifying MTHFR sequence abnormalities and specifically teaches the use of allele specific oligonucleotide hybridization probes in dot blot hybridization methods (page 18).

Additionally, Carlsson teaches nucleic acid hybridization methods to detect the presence of a polymorphism wherein the methods involve contacting a nucleic acid sample with an allele specific probe, hybridizing the probe to nucleic acids present in the sample and detecting the presence of hybridization between the probe and the nucleic acids (see, for example, column 3-4). Carlsson also teaches that detection probes can be used to rapidly and effectively analyze

multiple samples of nucleic acids simultaneously for the presence of polymorphisms (see, for example, columns 4 and 10).

In view of the teachings of Carlsson, it would have been obvious to one of ordinary skill in the art at the time the invention was made to have modified the method of Rozen so as to have detected the 677T (668T) polymorphism by hybridization using a probe in order to have provided a rapid and effective means for screening for the 677T (668T) in MTHFR nucleic acids.

With respect to claims 186, 187, 194-197, Rozen doesn't teach MTHFR probes of less than 50 nucleotides. However, Carlsson (see, for example, column 7 and claims 6 and 7) teaches that the detection probes may be of any length and are preferentially 10 or 15 nucleotides in length. Accordingly, it would have been obvious to one of ordinary skill in the art at the time the invention was made to have generated probes containing the 677T (668T) polymorphism wherein the probes were of a length of less than 50 nucleotides because Carlsson teaches that such probes allow for the effective detection of a polymorphism in a target nucleic acid.

With respect to claims 189 and 199, Rozen does not teach the use of PNA probes. However, Carlsson (columns 4-5) teaches that PNA probes may be used to detect the presence of a polymorphism. Carlsson teaches that PNA probes are advantageous because (i) PNA/DNA duplexes have a higher thermal stability than DNA/DNA duplexes, (ii) PNA/DNA duplexes are more sensitive to single base pair mismatches than DNA/DNA duplexes, and (iii) PNA/DNA duplexes form at a faster rate than DNA probes. Accordingly, it would have been obvious

to one of ordinary skill in the art at the time the invention was made to have generated PNA probes containing the 677T (668T) polymorphism in order to have achieved the advantages set forth by Carlsson of generating probes that would be more effective at detecting the presence of the 677T (668T) polymorphism in a target nucleic acid.

With respect to claims 190, 191, 200 and 201, Rozen does not specifically exemplify labeling the probes for detection of the 677T (668T) polymorphism. However, Carlsson teaches that the probes may be labeled with a fluorescent moiety (column 10). Accordingly, it would have been obvious to one of ordinary skill in the art at the time the invention was made to have labeled the MTHFR nucleic acids of Rozen containing the 677T (668T) polymorphism with a fluorescent moiety in order to have facilitated detection of hybridization between the probe and target nucleic acid.

7. Claims 186-187, 190-198, 200 and 201 are rejected under 35 U.S.C. 103(a) as being unpatentable over by van der Put in view of Shultz (U.S. Patent No. 6,235,480).

van der Put (see Table 1 and page 1045) teaches an isolated MTHFR nucleic acid which contains either an A or a C at nucleotide position 1298. The 1298 polymorphism disclosed by van der Put is identical to the presently claimed C1289A polymorphism (see the 132 Declaration of Dr. Stanton filed November 13, 2002 regarding the numbering of the nucleotides in SEQ ID NO: 1). Van der Put (page 1246) also teaches isolated MTHFR nucleic acids which contain both a T at position 677 (668) and an A at position 1298 (1289). van der Put teaches a

PCR fragment of 163 bp that contains the 1298A (1289A) polymorphism (see page 1045). The reference (pages 1045-1046) teaches that the 677T (668T) and 1298A (1289A) polymorphisms may be detected using PCR / restriction enzyme analysis and by sequencing. van der Put does not specifically exemplify hybridization methods using a probe containing the 677T (668T) polymorphism and/or the 1298A (1289A) polymorphism.

However, Shultz (see, for example, columns 51-52) teaches nucleic acid hybridization methods to detect the presence of a polymorphism wherein the methods involve contacting a nucleic acid sample with a probe, hybridizing the probe to nucleic acids present in the sample and detecting the presence of hybridization between the probe and the nucleic acids.

In view of the teachings of Shultz, it would have been obvious to one of ordinary skill in the art at the time the invention was made to have modified the method of van der Put so as to have detected the 677T (668T) and 1298A (1289A) polymorphisms by hybridization using a probe containing both of these polymorphisms in order to have provided a rapid and effective means for screening for the 677T (668T) and/or 1298A (1289A) polymorphisms simultaneously in MTHFR nucleic acids.

With respect to claims 186, 187, 194-197, van der Put does not teach MTHFR probes of less than 50 nucleotides. However, Shultz (column 52) teaches that the probes may be single stranded DNA of varying lengths, and particularly of a length of 10 to 30 nucleotides. Therefore, it would have been obvious to one of ordinary skill in the art at the time the invention was made to

have generated probes containing the 677T (668T) or the 1298A (1289A) polymorphism wherein the probes were of a length of less than 50 nucleotides because Shultz teaches that such probes allow for the effective detection of a polymorphism in a target nucleic acid.

With respect to claims 190, 191, 200 and 201, van der Put does not specifically exemplify labeling the probes for detection of the 677T (668T) or 1298A (1289A) polymorphism. However, Shultz teaches that any type of detectable moiety may be used to label the probes, including fluorescent dyes. Accordingly, it would have been obvious to one of ordinary skill in the art at the time the invention was made to have labeled the MTHFR nucleic acids of van der Put containing the 677T (668T) or 1298A (1289A) polymorphism with a fluorescent moiety in order to have facilitated detection of hybridization between the probe and target nucleic acids.

With respect to claims 190, 191, 193, 200 and 201, van der Put does not specifically exemplify methods for detecting both the 677T (668T) and the 1298A (1289A) polymorphism or labeled probes containing both of these polymorphisms. However, Shultz (column 52) teaches that the probes may be single stranded DNA of varying lengths, and particularly of a length of up to about 1000 nucleotides. Accordingly, it would have been obvious to one of ordinary skill in the art at the time the invention was made to have generated larger probes containing both the 677T (668T) and the 1298A (1289A) polymorphisms and to have used these probes in the hybridization method in order to have allowed for the simultaneous analysis of both polymorphisms.

8. Claims 189 and 199 are rejected under 35 U.S.C. 103(a) as being unpatentable over by van der Put in view of Shultz and further in view of Carlsson et al (U.S. Patent No. 6,020,126)

The teachings of van der Put and Shultz are presented above. The combined references do not teach using PNA probes to detect the MTHFR the 677T (668T) or 1298A (1289A) polymorphisms.

However, Carlsson (columns 4-5) teaches that PNA probes may be used to detect the presence of a polymorphism. Carlsson teaches that PNA probes are advantageous because (i) PNA/DNA duplexes have a higher thermal stability than DNA/DNA duplexes, (ii) PNA/DNA duplexes are more sensitive to single base pair mismatches than DNA/DNA duplexes, and (iii) PNA/DNA duplexes form at a faster rate than DNA probes.

Accordingly, it would have been obvious to one of ordinary skill in the art at the time the invention was made to have generated PNA probes containing the 677T (668T) or 1298A (1289A) polymorphism or both polymorphisms in order to have achieved the advantages set forth by Carlsson of generating probes that would be more effective at detecting the presence of the 677T (668T) and 1298A (1289A) polymorphisms in a target nucleic acid.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Carla Myers whose telephone number is (571) 272-0747. The examiner can normally be reached on Monday-Thursday from 6:30 AM-5:00 PM. A message may be left on the examiner's voice mail

service. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Gary Benzion, can be reached on (571)-272-0782.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to (571) 272-0547.

Patent applicants with problems or questions regarding electronic images that can be viewed in the Patent Application Information Retrieval system (PAIR) can now contact the USPTO's Patent Electronic Business Center (Patent EBC) for assistance. Representatives are available to answer your questions daily from 6 am to midnight (EST). The toll free number is (866) 217-9197. When calling please have your application serial or patent number, the type of document you are having an image problem with, the number of pages and the specific nature of the problem. The Patent Electronic Business Center will notify applicants of the resolution of the problem within 5-7 business days. Applicants can also check PAIR to confirm that the problem has been corrected. The USPTO's Patent Electronic Business Center is a complete service center supporting all patent business on the Internet. The USPTO's PAIR system provides Internet-based access to patent application status and history information. It also enables applicants to view the scanned images of their own application file folder(s) as well as general patent information available to the public.

For all other customer support, please call the USPTO Call Center (UCC) at 800-786-9199.

Carla Myers
June 22, 2004

CARLA J. MYERS
PRIMARY EXAMINER